REMARKS

Claims 6, 7, 9-11, 13, 15, 38, 39, 44-49, 53, 54, 66, 70, 71, 73, 75, 76, 78, 80, 81, 83, and 89-121 are pending. Claim 67 was cancelled in a non-responsive amendment filed on May 29, 2007 and is cancelled again here since the amendment was found to be non-compliant.

Claims 38 and 39 have been amended to incorporate a definition for R^7. This definition is taken from original claim 2, which was cancelled. Claim 38 has also been amended to correct the typographical error identified by the examiner. Claim 6 has been amended to refer to claim 38, instead of cancelled claim 2 ^ The examiner's identification of these errors is appreciated.

Claim 66 has been amended to depend on claim 38 such that the compounds defined therein are more definite. Claim 90 has been amended to broadly define a method for "inhibiting raf kinase in a human or other mammal" instead of treating a raf mediated disorder. This method is supported by the language that appears on page 2, line 14 of the specification. The objection to claim 38, the first rejection under 35 USC §112, second paragraph of claims 6 and 13, and the second rejection under 35 USC §112, second paragraph of claims 6, 10, 11, 13, 38, 39, 44-49, 53, 54, 70, 71, 75, 76, 80, and 81 are moot following the amendments above.

Information Disclosure Statement

Applicants acknowledge the deficiencies in the Information Disclosure Statement filed on June 14, 2006 and have submitted new 1449 forms with complete citations where possible. The publication date for the chapter authored by Lemoine is unknown. The citations in the chapter include those dated 1991, so the date indicated on the 1449 is "post 1991."

Enablement

Applicants maintain all pending claims clearly satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants also maintain the *Wands* factors related to this invention have not been properly characterized, particularly as to the state of the prior art, the breadth of the claims, the amount of direction provided and the quantity of experimentation needed.

State of the art

It is alleged that the nature of the art is unpredictable. The examiner cites two references, Gura et al. and Johnson et al. to support this position. These articles discuss alleged deficiencies in preclinical models and systems for identifying new drugs in general. There is no indication the assays described in the present application for identifying raf kinase inhibition are ineffective or defective or that the activity of the urea compounds applicants tested with this assay would not be expected to be efficacious. The language within Johnson et al. the examiner refers to relates to a particular xenograft assay and not the art of treating cancer in general. Naturally there is some uncertainty with all pharmaceuticals, which is the reason for clinical trials. The articles cited by the examiner do not show or suggest the compounds claimed are not efficacious. Furthermore, any uncertainty can be addressed with routine testing.

It is also alleged that "there is no evidence of record of analogous activity for similar compounds." However, applicants have cited earlier published applications (WO 98/52558, WO 99/32100, WO 99/32436 and WO 99/32455), assigned to the same assignee as the present invention, which disclose and claim aryl and hetaryl ureas that inhibit raf kinase and find use in treating cancer. Applicants have also cited the work of others, e.g., US 5,773,459; US 6,143,764, and WO 97/40028.

Claim breadth

The claims herein are not overly broad when considered as a whole. The compounds of this invention all have a required substituent (SO_2R_x, $-C(O)R_x$ or $-C(NR_y)\ R_z$) which appears on a particular moiety of the molecule, (L^1). The examples of this invention demonstrate activity can be maintained with variations in this substituent. The ability to vary other parameters (heterocycles) has been demonstrated in earlier applications (WO 98/52558, WO 99/32100, WO 99/32436 and WO 99/32455). The examiner focuses on variations in the ring structure and substituents which are possible and ignores the similarities. For example compound A on page 13 of the office action has a urea group, like Sorafenib, and a required substituent (SO_2NH_2) on a remote ring with a similar function to the substituent $C(O)NCH_3$ on Sorafenib.

Directions and Guidance

The specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of cancers. As noted by the examiner , the specification also provides dosage ranges for the various methods of administration on page 13. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited cancers with a compound of this invention.

The examiner requires the specification provide disclosure which is not necessary to satisfy the statute. More particularly, the examiner requires that the specification provide dosages, timing of administration and administration routes for each of the cancers claimed.

There is no requirement that an applicant provide any working examples relating to the treatment of every claimed disease to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, there is no requirement for any examples. The MPEP states that "compliance with the enablement

requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The examiner alleges that the inhibition of a receptor does not predictably correlate to clinical efficacy. No evidence has been presented to support this allegation and no evidence has been presented the assays described are not predictive. Clinical efficacy has been demonstrated with Sorafenib, which has been approved for the treatment of renal cancer. In addition, the clinical efficacy referred to by the Examiner is beyond what is necessary to satisfy the enablement requirement of 35 USC '112, first paragraph. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442, (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs will prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures in any crucial area such as the treatment of cancer.

This rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. As stated in *In re Anthony*, 414 F2d 1383, 162 USPQ 594, 604 (CCPA 1969), "Approval by the FDA, is not a prerequisite for the patenting of a new drug." As to the issue of safety, *In re Anthony* held,

> ...Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market, under the conditions prescribed, recommended or suggested in the proposed labeling thereof, as the majority of this court noted in *Hartop*, 135 USPQ at 426, 427.

Applicants maintain the specification provides more than it needs to, e.g., *in vitro* raf kinase assays (and IC_{50} data) and *in vivo* assays (see pages 94 and 96) and clearly satisfies the statutory requirements.

Experimentation

The examiner has ignored the contents of the disclosure and the level of skill in the art in alleging undue experimentation is required to practice the invention. The examiner has not identified any compound encompassed by the claims which can not be synthesized and tested by the methods provided in the application or known to those skilled in the art. The examiner equates routine testing with experimentation.

> As discussed in Wands, cited by the Examiner, "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

As stated above, the specification here provides more than it needs to, e.g., *in vitro* raf kinase assays (and IC_{50} data) and *in vivo* assays (see pages 94 and 96). In similar fashion, one of ordinary skill in the art by performing the same or similar tests, can determine the activity levels of each of the claimed compounds in treating various cancers. This is absolutely routine in the field.

The examiner alleges that the compounds synthesized do not correlate in scope with the compounds claimed. The examples in the application are not the only ureas which have been synthesized and tested for the inhibition of raf kinase. Applicants had the benefit of earlier work regarding various heterocycles and substituents on the urea compounds. The compounds exemplified in the application have one of the required substituents on L^1. Thus, appellants have provided more than an adequate number of examples to enable the claimed invention.

Given the extent of the disclosure provided, it would have most involved routine experimentation, if any at all, for one skilled in the art to treat any one of the recited cancers with a compound of this invention. Even absent the specification disclosure as discussed above, the rejection is clearly deficient under general controlling case law. The courts have placed a burden on the PTO to provide evidence shedding doubt on the disclosure that the

invention can be made and used as stated. See example *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

For the reasons discussed above, applicants submit all pending claims satisfy the requirements of 35 U.S.C. § 112, first paragraph.

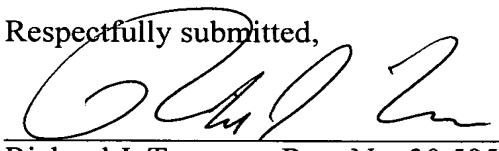
Obviousness-Type Double-Patenting

These provisional rejections will be addressed once claims herein are otherwise in condition for allowance.

In view of the above, favorable reconsideration is courteously requested. If there are any remaining issues which can be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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